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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,413	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 02, 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-71* is/are pending in the application.

4a) Of the above claim(s) *44-46,52-54 and 59-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-43, 47-51, 55-58 and 62-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/2004+04/02/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of species 5'TCG3' in the reply filed on 08/04/2006 is acknowledged.

Status of Claims

2. Claims 1-41 are cancelled. Claims 42-71 are added. Claims 44-46, 52-54 and 59-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/04/2006. Claims 42-43, 47-51, 55-58 and 62-71 are under examination.

Information Disclosure Statement/Petition

3. The Information Disclosure Statement (IDS) filed 01/14/2004 has been considered, along with a copy submitted on 04/02/2007, with the exception for 1 or 2 listed references. These references fail to comply with 37 C.F.R. 1.98 (b)(5), which requires: Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication. In the instant case, noncompliance with 37 C.F.R. 1.98 (b)(5) is noted for the following references: New England BIOLABS 1988-1989 Catalog, and Lagrange et al., Immune Responses Directed Against Infectious and Parasitic Agents, Principle Types of Immune Responses.

Beside those references, all the references cited on the noted IDS have been considered. In view of this, it should be noted that Applicant's petition regarding the IDS is moot.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 42-43, 47-51, 55-58 and 62-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the rejection, Applicant submits that Applicant has possession of a class of compounds, oligonucleotides comprising the CpG motif, which can be used according to the methods of the invention. To support this position, Applicant cited an excerpt from MPEP § 2162 and 2163, and asserts that Applicant does not have to demonstrate written description through actual reduction to practice or drawings.

Applicant's submission has been considered, however, it is not found persuasive. As presented in the excerpt provided by Applicant: Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing

distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

This excerpt sets forth that possession may be shown by actual reduction to practice or by the disclosure of drawings that show that the invention was complete. Hence, while Applicant may assert that Applicant does not have to show actual reduction to practice or drawings to satisfy the written description requirement, however, it remains that these factors are considered in determining possession under the written description requirement of 35 U.S.C. 112, first paragraph.

In the absence of evidence of possession through actual reduction to practice or by the disclosure of drawings that show that the invention was complete, Applicant must show possession of the claimed invention by describing distinguishing identifying characteristics. In the instant case, it is noted that Applicant is arguing that Applicant has demonstrated that Applicant is in possession of the claimed invention by describing distinguishing identifying characteristics and that Applicant is unaware of a requirement to set forth "functional characteristics" to meet the written description requirement.

With regard to Applicant's latter assertion, the Office directs Applicant's attention MPEP § 2163 (II)(3)(a)(i)(c) and the paragraph following it further clarify this requirement to include disclosure of complete or partial structure, physical and/or chemical properties, **functional characteristics**, correlation between structure and function, and methods of making the claimed invention. Thus, while Applicant may assert that Applicant is unaware of one of all of these requirements, these requirements are clearly set forth in MPEP § 2163.

Regarding Applicant's assertion hat Applicant has shown possession by describing distinguishing identifying characteristics, this submission has been considered, however, it is not found persuasive. In the instant case, as presented in the previous office action, the disclosure fails to provide relevant identifying characteristics relating to the claimed invention. The disclosure fails to set forth the complete structure of an oligonucleotide that treats, prevents or ameliorate papilloma viral infection. The disclosure does not even set forth the partial structure of oligonucleotides containing the CpG motif that treat, prevent or ameliorate papilloma viral infection. The disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention. Furthermore, the disclosure failed to set forth any functional characteristics that oligonucleotides containing the CpG motif must possess to treat, prevent or ameliorate papilloma viral infection. All that is present in the disclosure are oligonucleotides that are capable of stimulating the immune response. In all, nothing exists in the disclosure evidencing that any of the immunostimulatory oligonucleotides are capable of treating, preventing and ameliorating papilloma viral infection.

As previously presented, the claimed invention is directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

The basic inquiry for possession is: Can one skilled in the art reasonably conclude that the inventor was in possession of the claimed invention at the time the

application was filed? If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, *even if every nuance of the claim is not explicitly described in the specification*, then the requirement for an adequate written description is met.

To provide adequate written description and evidence of possession, the specification must provide sufficient description of the claimed invention by i) actual reduction to practice, ii) reduction to drawings; or iii) disclosure of relevant identifying characteristics, such as disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, and methods of making the claimed invention. The analysis:

i) Sufficient description of the claimed invention by actual reduction to practice: The only instance in which the specification refers to papilloma viral infection is on Line 21, page 14, wherein the specification lists papilloma viruses as one of the many examples of infectious virus. Beside that single reference to papilloma viruses, the specification does not teach anything else relating to papilloma viral infection and the use of an oligonucleotide comprising the CpG motif to treat, prevent or ameliorate the infection. Not a single oligonucleotide containing the CpG motif that treats, prevents or ameliorates papilloma viral infection is provided in the specification. In the instant, the disclosure fails to evidence that Applicant is in possession of the claimed invention by actual reduction to practice.

ii) Sufficient description of the claimed invention by reduction to drawings: The instant patent application is filed with many drawings. However, none of the drawings provided sets forth an oligonucleotide comprising the CpG motif that treats, prevents or ameliorate any viral infection, including papilloma viral infection. Hence, the disclosure fails to evidence that Applicant is in possession of the claimed invention by reduction to drawings.

iii) disclosure of relevant identifying characteristics: The disclosure fails to provide relevant identifying characteristics relating to the claimed invention. The disclosure fails to set forth the complete structure of an oligonucleotide that treats, prevents or ameliorate papilloma viral infection. The disclosure does not even set forth the partial structure of oligonucleotides containing the CpG motif that treat, prevent or ameliorate papilloma viral infection. The disclosure further failed to set forth the physical and chemical properties of oligonucleotides encompassed by the claimed invention. Furthermore, the disclosure failed to set forth any functional characteristics that oligonucleotides containing the CpG motif must possess to treat, prevent or ameliorate papilloma viral infection.

In the instant, nothing exists in the specification to demonstrate that Applicant is in possession of an oligonucleotide containing the CpG motif that treats, prevents and ameliorate any viral infection, including papilloma viral infection. In the absence of any

evidence demonstrating that Applicant is in possession of the primary active ingredient for the claimed invention, oligonucleotides comprising the CpG motif that treat, prevent or ameliorate papilloma viral infection, the skilled artisan cannot reasonably conclude or recognize that Applicant is in possession of the claimed invention at the time the invention was filed.

Applicant is reminded that that written description requirement is separate and distinct from the enablement requirement.

6. Claims 42-43, 47-51, 55-58 and 62-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the rejection, Applicant submits that the specification is enabling for the claimed invention. Applicant submits that Applicant have demonstrated, via working examples, that oligonucleotides containing the CpG motif are effective in inducing a pattern of immune stimulation that is consistent with the treatment of viral infection. To support this position Applicant notes that Applicant has provided examples in the specification that show production of antibody response to oligonucleotide stimulation, stimulation of B cells, natural killer cells and monocytic cells, and production of IFN-gamma and as well as other cytokines. Applicant further notes that the specification asserts that CpG oligonucleotides are useful in treating viral infections, including papilloma viral infection, and that the combination of the changes in immune

parameters demonstrated with the oligonucleotides is sufficient to support Applicant's assertion that the oligonucleotides would be useful in the treatment of papilloma viral infection.

Applicant's submission has been considered, however, it is not found persuasive. As Applicant has presented, all that Applicant has provided in the specification is an **assertion** that the immunostimulatory oligonucleotides are useful in the treatment of viral infection, including papilloma viral infection. Applicant has not set forth any evidence setting forth that such oligonucleotides are indeed therapeutic against viral infection. Moreover, Applicant has not set forth any guidance teaching the skilled artisan how to harness the immunostimulatory activities to render a therapeutic efficacy against viral infection. All that Applicant has shown is that the oligonucleotides are immunostimulatory and an assertion, which is not substantiated by any evidence demonstrating that the oligonucleotides are therapeutic against viral infection, that the oligonucleotides are useful in treating viral infections.

In addition to above, Applicant submits that Applicant has provided sufficient direction and guidance in the specification. To support this position, Applicant submits that Applicant has described the structural properties of the oligonucleotides and has taught that they can be used to treat viral infection, including papilloma viral infection.

Applicant's submission has been considered, however, it is not found persuasive. While it is true that Applicant has described the structural properties of the oligonucleotides, however, it should be noted that the structural properties that are taught in the specification is related to the immunostimulatory activities of the

oligonucleotides. Applicant has not taught of a single oligonucleotide that is therapeutic against viral infection, including papilloma virus. Hence, in the absence of any guidance directing to oligonucleotides having therapeutic efficacy against viral infection, including papilloma viral infection, Applicant has not provided sufficient direction and guidance to enable the skilled artisan to practice the claimed invention without undue experimentation.

Additionally, Applicant objected to the Office conclusion that all that is present in the specification are conjectures of potential application of such oligonucleotides against viral infection, and requested the Office to substantiate this position.

Applicant's objection has been noted, however, the Office stands by this position. In this case, Applicant has not shown or taught that an oligonucleotide comprising the CpG motif has a therapeutic affect against viral infection. All that Applicant has shown is that these oligonucleotides are immunostimulatory, and from these immunostimulatory activities, Applicant asserts that they are useful in the treatment of viral infections. Applicant has not substantiated this assertion by any facts that correlates and commensurate with the claimed invention. As mentioned, the claimed invention is specifically directed at treating, preventing and ameliorating papilloma viral infection. However, Applicant has not taught or provided any guidance directing at the type of immunoparameter that must be modulated, which oligonucleotide has this immunomodulatory activity, and the extent in which the modulation must occur to render a therapeutic affect against papilloma viral infection. All that is present is an assertion

of use without any substantiating evidence. Similarly, all that is present are conjectures, reasoning that involve the formation of conclusions from incomplete evidence, of use.

Applicant further submits that much of the art cited in the enablement are not relevant to the current claimed invention. Applicant also asserts that there is no evidence of unpredictability of the invention.

Applicant's submission has been considered, however, it is not found persuasive. It should be noted that the claimed invention is directed at the treatment of papilloma infection with the administration of a CpG oligonucleotide. At the time the invention was made, it is well known in the art that the CpG motif present in the oligonucleotide stimulates Th1 immune response, which induces the production of Th1 associated cytokines. In the instant case, while the claimed invention does not specifically recites the administration of a cytokine, it does relies on the production of a Th1 associated cytokines to render a therapeutic efficacy for a disease. Hence, the cytokine art was introduced in the enablement rejection to demonstrate the level of unpredictability and the quantity of experimentation that would be required of the skilled artisan attempting to practice the claimed invention. In the instant case, the Office relies on the cytokine art to establish that the skilled artisan would not be able to practice the claimed invention without an undue burden of experimentation.

In all, Applicant is reminded that the enablement rejection is made on the basis of the Wands factors. In view of the Wands factors, as established in the previous office action, it is found that the specification is not enabling for the claimed invention. While Applicant may argue that the specification is enabling, the evidence as a whole

evidences that Applicant has enabled the skilled artisan to practice the claimed invention without undue experimentation. Applicant has not provided a single working example that is directed at demonstrating at an oligonucleotide comprising the CpG motif is therapeutic against papilloma viral infection, nor any guidance evidencing that said oligonucleotide is indeed therapeutic against papilloma viral infection. This is further exemplified by Applicant's submission, wherein Applicant repeatedly asserted that Applicant teaches the use of the oligonucleotide to induce an immune response. And, Applicant is reminded that this teaching does not commensurate in scope with the claimed invention.

As previously presented, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the claims:

The claimed method of treating, preventing or ameliorating papilloma viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject.

The specification provides the following, A "subject" shall mean human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse. [Lines 31-32, page 19.]

Hence, the breadth of the claims is directed to a method of treating, preventing or ameliorating papilloma viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject. The subjects encompassed by the claimed invention are all vertebrate animals, including humans.

Presence or Absence of working examples:

The specification does not contain any working examples that are directed to the claimed invention, a method of treating, preventing or ameliorating papilloma viral infection in a subject with the administration of an oligonucleotide comprising the CpG motif. The specification does not containing any working examples demonstrating that such oligonucleotides treat, prevent or ameliorate any viral infection. Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicant's claimed invention, wherein oligonucleotides comprising the CpG motif treat, prevent or ameliorate viral infection, including papilloma viral infection.

Amount of direction or guidance present in the specification:

The specification only refers to papilloma virus once, line 21, page 14. Beside this single reference to the virus, the specification does not contain any teachings relating to the virus. In the instant, the specification does not set forth any evidence demonstrating that oligonucleotides containing the CpG motif treat, prevent or ameliorate viral infection. All that is present in the specification are conjectures of potential application of such oligonucleotides in the treatment, prevention and amelioration of viral infections in vertebrate subjects. However, none of these conjectures are substantiated by any evidence.

Nature of the invention

Based on Applicant's disclosure, it appears that the nature of the claimed invention is directed to the use of the art recognized immunostimulatory activity of oligonucleotides containing the CpG motif, including the induction of Th1 immune response invoked by the production of Th1 associated cytokines, accorded by the CpG motif, to render a therapeutic value, wherein the desired therapeutic value is to provide treatment, prevention and amelioration of papilloma viral infection in vertebrate subject--immunotherapy.

State of the Art:

In the instant, the involvement of a Th1 type immune response in combating against intracellular pathogens is a well-recognized general concept. The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular

Th1-associated cytokine to the treatment, prevention and amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious diseases, the production of the "right" set of cytokines can be a matter of life or death, as noted by Infante-Duarte et al. Infante-Duarte et al. further notes that in addition to a Th1 type immune response, a Th2 type immune response is also necessary. Specifically, Infante-Duarte et al. teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the Th1 type immune response from causing damage to the host.[1] Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection.

The cytokine art also provides that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12 and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al.,[2] Bohn et al.,[3] Sakao et al.,[4] Zaitseva et al.,[5] and Masihi, K.[6] Aoki et al. teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2

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[1] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[2] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[3] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]
[4] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[5] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]

does not confer protection for virulent *M. bovis* infection. Bohn et al. teaches that interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice. Sakao et al. teaches that interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. Zaitseva et al. teaches that both interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection. Masihi, K. notes that interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. In summation, the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated.

Additionally, while the art teaches that oligonucleotides containing the CpG motif are capable of stimulating a Th1 type immune response, however, the art also teaches that the Th1 associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next, as evidenced by Krieg et al. [7] and

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[6] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]

[7] Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [paragraph that bridge pages 716-717, in particular.]

Mutwiri et al.[8] Krieg et al notes that each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Krieg et al. particularly notes that the type of cytokine stimulated by oligonucleotides containing the CpG motif is distinct from one oligonucleotide to the next. Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacings between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence.

The CpG art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically, Mutwiri et al. notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.

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[8] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90.]

Furthermore, both Krieg et al. and Mutwiri et al. sets forth that the recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al. provides that TLR-9 has only been identified in mice and humans. Mutwiri et al. also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9, then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one species to the next. Mutwiri et al. also sets forth that *in vitro* observations do not accurately predict what happens *in vivo*.

Moreover, the potential use of oligonucleotides containing the CpG motif to stimulate a Th1 type immune response that treats and prevents infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive, as evidenced by Yamamoto et al.,[9] Equils et al.,[10] Agrawal et al.,[11] and Olbrich et al.[12] Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza. Equils et al. teaches that such oligonucleotides can induce the HIV transcriptional regulatory elements in long terminal

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[9] Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40.
[10] Equils et al. Toll-like receptor 2 (TLR2) and TLR9 signaling resulted from HIV-long terminal repeat transactivation and HIV replication in HIV-1 transgenic mouse spleen cells: implications of simultaneous activation of TLRs on HIV replication. J. Immunol. 2003, 170, 5159-5164.
[11] Agrawal, et al. Was induction of HIV1 through TLR9? J. Immunol. 2003, 171, 1621-1621.
[12] Olbrich et al. Preinfection treatment of resistant mice with CpG oligodeoxynucleotides renders them susceptible to friend retrovirus-induced leukemia. J. Virol., 2003, 77, 10658-10662.

repeats, increasing viral replication. Agrawal et al. teaches that HIV-infected humans treated with oligonucleotides containing the CpG motif showed dose-dependent increases viral load. Lastly, Olbrich et al. teaches that the administration of oligonucleotides containing the CpG motif accelerated and increased the severity of Friend retrovirus in mice. In the case of Olbrich et al., the author notes that the use of oligonucleotides containing the CpG motif for the treatment of viral infection may be a double edge sword that can resolute in effective therapy but also in acceleration of disease. Olbrich et al. notes that this double edge sword observation may be dependent on the time point of treatment.

Hence, overall, the literature notes the use of CpG to stimulate the production of cytokines, the use of cytokines to influence viral infection, and the development of a treatment regimen for diseases is unpredictable and complicated.

Additionally, the papilloma viral art also notes the failure of oligonucleotides comprising the CpG motif to demonstrate any therapeutic effect on papilloma growth, as evidenced by Poetker et al.[13] Poetker et al. also notes that the lack of a therapeutic effect by the oligonucleotide suggests that either enhanced papilloma antigen presentation or targeting of immune evasive mechanisms used by the papillomas is needed to treat bulky disease with an immunotherapeutic strategy. And Poetker et al. further notes that such mechanism will need to be addressed if immunotherapeutic strategies are to be rationally and successfully applied. In the instant, while the claimed invention utilizes immunotherapeutic approach, it is noted that the immunotherapeutic

strategy does not include an enhanced papilloma antigen presentation or targeting of immune evasive mechanisms used by the papillomas. None of these factors are present in the claimed invention.

Predictability or unpredictability of the art:

As discussed above, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. The art also recognizes that use of CpG to stimulate cytokine production, the use of the induced cytokine to influence viral infection, and the development of treatment regimen unpredictable and complicated. The art additionally teaches that the efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive.

Quantity of experimentation necessary:

Extreme undue burden of experimentation would be imposed upon the skilled artisan practicing the claimed invention. As stated above, Applicant has not provided much, if any, guidance or direction relating to the claimed invention. All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that are well known in the art. And the formation of a conclusion based on generalized concepts renders the conclusion flawed. Generalized concepts are directed to support a general direction of studies or research; however, they do not support concrete conclusions. Concrete conclusions must be substantiated by facts, including evidence. In the instant, while the general direction of research may be outlined for the skilled artisan, the skilled

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[13] Poetker et al. Immune Stimulation for the treatment of papilloma. Annals of Otology: Rhinology &

artisan would not readily be able to practice the claimed invention without the undue burden of experimentation. The path that the skilled artisan must take in his research is marked with many challenges that are recognized in the art, including the complex nature of oligonucleotides containing CpG motif and the complexity of the immune system, including the Th1 type immune response and the functional characteristics of its associated cytokines. Hence, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat, prevent or ameliorate viral infection in a subject; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan would not be able to reasonably practice the claimed invention without an undue burden experimentation. Thus, the claims are rejected under 35 U.S.C § 112, 1st paragraph for failing to comply with the enablement requirement.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. In response to all the provisional double patenting rejections, Applicant submits that the rejection will be addressed when the claimed invention is allowed.

Applicant's submission has been considered, however, until the rejections are properly addressed, the rejections are maintained.

9. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 97, of copending Application No. 10/613524.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 97 of the conflicting patent application is directed at a method for preventing a disease in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: Claim 97 of the conflicting patent application is not limited to the prevention of papilloma viral infection in a subject. However, it is noted that by "disease", the conflicting patent application also intends to encompass infectious diseases. [See claim 40 of the conflicting patent application] Thus, by the term "disease", the conflicting patent application intends to encompass infectious disease. And the specification, paragraph 22 of the PreGrant publication, of the conflicting application discloses papilloma viral infection as an infectious disease. Thus, by disease, claim 97 of the conflicting patent application also encompasses papilloma viral infection, which is an infectious disease.

The other difference between the claims is: claim 97 of the conflicting patent application is directed to specific species of oligonucleotide, SEQ ID NO: 1, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 97 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 97 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 37, of copending Application No. 10/894862.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 37 of the conflicting patent application is directed at a method of treating an infection in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: claim 37 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject.

However, it is noted that by "infection", claim 37 of the conflicting patent application includes viral infection. And paragraph 49 of the conflicting patent application's PreGrant publication provides papilloma viral infection as a viral infection. Hence, by infection, claim 37 of the conflicting patent application also encompasses papilloma viral infection.

The other difference between the claims is: claim 37 of the conflicting patent application is directed to a species of oligonucleotide, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 37 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 37 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19, of copending Application No. 10/987146.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 37 of the conflicting patent application is directed at a method of treating viral infection in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: claim 19 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, paragraph 49 of the conflicting patent application's PreGrant publication provides papilloma viral infection as a viral infection. Hence, by viral infection, claim 19 of the conflicting patent application also encompasses papilloma viral infection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 42, of copending Application No. 10/382822.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 42 of the conflicting patent application is directed at a method of treating, preventing and ameliorating viral infection in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: claim 42 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject.

However, paragraph 49 of the conflicting patent application's PreGrant publication provides papilloma viral infection as a viral infection. Hence, by viral infection, claim 42 of the conflicting patent application also encompasses papilloma viral infection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 59, of copending Application No. 11/255100.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 59 of the conflicting patent application is directed at a method for treating an infectious disease in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: Claim 59 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, it is noted that by "infectious disease", the conflicting patent application also intends to encompass viral infection. [See claim 60 of the conflicting patent application] Thus, by the term "infectious disease", the conflicting patent application intends to encompass viral infection. And the specification, paragraph 59 of the PreGrant publication, of the conflicting application discloses papilloma viral infection as an

infectious disease. Thus, by infectious disease, claim 59 of the conflicting patent application also encompasses papilloma viral infection.

The other difference between the claims is: claim 59 of the conflicting patent application is directed to specific species of oligonucleotide, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 59 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 59 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 42-43, 47-51, 55-58 and 62-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 45, of copending Application No. 11/361313.

Claims 42-43, 47-51, 55-58 and 62-71 are directed toward a method of treating, preventing and ameliorating papilloma viral infection with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to a subject having papilloma viral infection.

Claim 45 of the conflicting patent application is directed at a method for treating an infectious disease in a subject with the administration of an oligonucleotide comprising the CpG.

The difference between the claims is: Claim 45 of the conflicting patent application is not limited to the treatment of papilloma viral infection in a subject. However, it is noted that by the term "infectious disease", the conflicting patent application intends to encompass viral infection. [Paragraph 39 of the PreGrant publication of the conflicting application] At the cited passage, the specification of the conflicting patent application discloses papilloma viral infection as an infectious disease. Thus, by infectious disease, claim 45 of the conflicting patent application also encompasses papilloma viral infection.

The other difference between the claims is: claim 45 of the conflicting patent application is directed to specific species of oligonucleotide, whereas, the claims of the instant patent application is directed to a genus of oligonucleotides. In the instant, the species of oligonucleotide recited in claim 45 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Hence, the species of oligonucleotide recited in claim 45 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Some of the above rejections are, in part, based on the specification of the conflicting patent application, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II(B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of

the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.

The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

Conclusion

15. No claims are allowed.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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